79. CLAIMS

We claim:

1. A method of diagnosing an abnormality in endometrial glandular development in a woman suspected of being infertile comprising the step of:

detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from on or after day 20 of an idealized 28 day menstrual cycle from a woman suspected of being infertile;

wherein

expression of cyclin E in the nuclei of greater than 5% of the gland cells indicates endometrial glandular developmental arrest, and/or

expression of cyclin E of greater than 1+ staining intensity in the cytoplasm of greater than 10% of the gland cells indicates endometrial glandular developmental arrest.

2. The method of claim 1 wherein the expression of cyclin E is detected by an immunohistochemisty assay.

3. The method of claim 1 wherein the cycle day is determined by examining the stroma cells in the sample.

4. The method of claim 1 wherein expression of cyclin E is detected in the nuclei of greater than 10% of the gland cells in the sample is indicative of endometrial glandular developmental arrest.

5. The method of claim 1 wherein the cycle day is day 24 of an idealized 28 day menstrual cycle.

6. The method of claim 1 further comprising the step of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample.

7. The method of claim 1 further comprising the step of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample.

8. The method of claim 1 further comprising the step of detecting the expression mouse ascites golgi mucin MAG in the gland cells in a serial section of the sample.

9. The method of claim 1 further comprising the steps of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample and either detecting the expression of progesterone receptor in the gland cells in a serial section of the sample or detecting the expression of MAG in the gland cells in a serial section of the sample or both.

10. The method of ~~claim~~ 1 further comprising the step of detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

11. The method of claim 1 further comprising the step of detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from day 15 an idealized 28 day menstrual cycle from the woman.

12. The method of ~~claim~~ 1 further comprising the step of detecting expression of p27 in the nuclei of endometrial gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

13. The method of claim 1 further comprising the step of detecting expression of p27 in the nuclei of endometrial gland cells in an endometrial tissue sample from before day 17 of an idealized 28 day menstrual cycle from the woman wherein expression of p27 is indicative of accelerated endometrial glandular development.

14. The method of claim 1 further comprising the step of detecting expression of progesterone receptor in the gland cells in an endometrial tissue sample from before day 18 of an idealized 28 day menstrual cycle from the woman.

15. The method of claim 1 further comprising the step of detecting the expression of MAG in the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

16. The method of claim 1 further comprising at least two of the following steps of:

a) detecting the expression of cyclin E in the nuclei and/or cytoplasm of the gland cells in an endometrial tissue sample from on or before day 18 of a an idealized 28 day menstrual cycle from the woman;

b) detecting the expression of p27 in the nuclei of gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

c) detecting expression of progesterone receptor in gland cells in an endometrial tissue sample on or before day 18 of an idealized 28 day menstrual cycle from the woman;

d) detecting the expression of MAG in the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

wherein said two or more steps are performed on serial sections of the sample.

17. A method of predicting abnormal endometrial glandular development comprising the steps of :

detecting the level of p27 in the nuclei of cells in a sample of endometrial tissue from day 10-18 of a an idealized 28 day menstrual cycle from a woman suspected of being infertile, and

comparing the level of expression with an expected level of expression;

wherein detection of elevated levels of p27 in the sample is predictive that the woman will be diagnosed with endometrial glandular developmental arrest.

18. The method of claim 17 wherein the expression of p27 is detected by an immunohistochemisty assay.

19. The method of claim 17 wherein the cycle day is determined by examining the stroma and gland cells in the sample.

20. The method of claim 17 wherein the cycle day is day 15 of a an idealized 28 day menstrual cycle.

21. The method of claim 17 further comprising the step of detecting the expression of cyclin E in the nuclei and /or cytoplasm of gland cells in a serial section of the sample.

22. The method of claim 17 further comprising the step of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample.

23. The method of claim 17 further comprising the step of detecting the expression MAG in the gland cells in a serial section of the sample.

24. The method of claim 17 further comprising at least two of the following steps of:

a) detecting the expression of cyclin E in the nuclei and/or cytoplasm of the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

b) detecting expression of progesterone receptor in gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

c) detecting the expression of MAG in the gland cells in an endometrial tissue sample on or before day 18 of an idealized 28 day menstrual cycle from the woman;

wherein said two or more steps are performed on serial sections of the sample.

25. A method of assessing the suitability of the endometrium for embryo implantation in a woman undergoing ovulation induction comprising the step of:

detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from before day 17 of an idealized 28 day menstrual cycle;

wherein

expression of cyclin E in the nuclei of greater than 5% of the gland cells indicates the endometrium is unsuitable for embryo implantation; and/or

expression of cyclin E of 2-3+ staining intensity in the cytoplasm of less than 50% of the gland cells indicates the endometrium is unsuitable for embryo implantation.

26. The method of claim 25 wherein the expression of cyclin E is detected by an immunohistochemisty assay.

27. The method of claim 25 wherein the cycle day is determined by examining the stroma and gland cells in the sample.

28. The method of claim 25 wherein expression of cyclin E is detected in the nuclei of greater than 10% of the gland cells in the sample indicates the endometrium is unsuitable for embryo implantation.

29. The method of claim 25 wherein the cycle day is day 15 of an idealized 28 day menstrual cycle.

30. The method of claim 25 further comprising the step of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample wherein detection of expression of p27 in the nuclei of greater than 0% of the gland cells in the sample indicates the endometrium is unsuitable for embryo implantation.

31. The method of claim 25 further comprising the step of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample wherein detection of expression of p27 in the nuclei of greater than 5% of the gland cells in the sample indicates the endometrium is unsuitable for embryo implantation.

32. The method of claim 25 further comprising the step of detecting the expression of progesterone receptor in less than 10% of the gland cells in a serial section of the sample.

33. The method of claim 25 further comprising the step of detecting the expression MAG in the gland cells in a serial section of the sample wherein detection of expression of MAG in less than 10% of the gland cells in the sample indicates the endometrium is unsuitable for embryo implantation.

34. The method of claim 25 further comprising the steps of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample and either detecting the expression of progesterone receptor in the gland cells in a serial section of the sample or detecting the expression of MAG in the gland cells in a serial section of the sample or both.

35. The method of claim 25 further comprising at least two of the following steps of:

a) detecting the expression of p27 in the nuclei of gland cells in an endometrial tissue;

b) detecting expression of progesterone receptor in gland cells in an endometrial tissue sample;

c) detecting the expression of MAG in the gland cells in an endometrial tissue sample;

wherein said two or more steps are performed on serial sections of the sample.

36. The method of claim 25 wherein the woman is undergoing ovulation induction as part of a procedure selected from the group consisting of: IVF following hyperstimulation, IUI following clomiphene hyperstimulation; ZIFT following hyperstimulation and GIFT following hyperstimulation.

37. A method of evaluating the effect of a hormonal protocol on endometrial glandular development in a woman undergoing a hormonal protocol to produce a mock cycle, said method comprising the steps of:

detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from on or after day 20 of an idealized 28 day menstrual cycle from a woman undergoing a hormonal protocol to produce a mock cycle; and

wherein

expression of cyclin E in the nuclei of greater than 5% of the gland cells indicates endometrial glandular developmental arrest, and/or

expression of cyclin E of greater than 1+ staining intensity in the cytoplasm of greater than 10% of the gland cells indicates endometrial glandular developmental arrest.

38. The method of claim 37 wherein the expression of cyclin E is detected by an immunohistochemisty assay.

39. The method of claim 37 wherein expression of cyclin E is detected in the nuclei of greater than 10% of the gland cells in the sample is indicative of endometrial glandular developmental arrest.

40. The method of claim 37 wherein the cycle day is day 24 of an idealized 28 day menstrual cycle.

41. The method of claim 37 further comprising the step of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample.

42. The method of claim 37 further comprising the step of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample.

43. The method of claim 37 further comprising the step of detecting the expression MAG in the gland cells in a serial section of the sample.

44. The method of claim 37 further comprising the steps of detecting the expression of p27 in the nuclei of gland cells in a serial section of the sample and either detecting the

expression of progesterone receptor in the gland cells in a serial section of the sample or detecting the expression of MAG in the gland cells in a serial section of the sample or both.

45. The method of claim 37 further comprising the step of detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

46. The method of claim 37 further comprising the step of detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from day 15 of an idealized 28 day menstrual cycle from the woman.

47. The method of claim 37 further comprising the step of detecting expression of p27 in the nuclei of endometrial gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

48. The method of claim 37 further comprising the step of detecting expression of p27 in the nuclei of endometrial gland cells in an endometrial tissue sample from before day 17 of an idealized 28 day menstrual cycle from the woman wherein expression of p27 of greater than 0% is indicative of accelerated endometrial glandular development.

49. The method of claim 37 further comprising the step of detecting expression of progesterone receptor in the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

50. The method of claim 37 further comprising the step of detecting the expression of MAG in the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman.

51. The method of claim 36 further comprising at least two of the following steps of:

a) detecting the expression of cyclin E in the nuclei and/or cytoplasm of the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

b) detecting the expression of p27 in the nuclei of gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

c) detecting expression of progesterone receptor in gland cells in an endometrial tissue sample on or before day 18 of an idealized 28 day menstrual cycle from the woman;

d) detecting the expression of MAG in the gland cells in an endometrial tissue sample from on or before day 18 of an idealized 28 day menstrual cycle from the woman;

wherein said two or more steps are performed on serial sections of the sample.

52. The method of claim 37 further comprising the step of adjusting the hormonal protocol following evaluation.

53. The method of claim 52 further comprising the step of repeating the evaluation method in a second mock trial following the adjusting of the hormonal protocol.

54. A method of evaluating a hormone replacement therapy protocol in a woman undergoing hormone replacement therapy, said method comprising the steps of :

detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from said woman;

detecting expression of p27 in the nuclei an of endometrial gland cells in serial section of said endometrial tissue sample;

wherein

expression of cyclin E in the nuclei of greater than 5% of the gland cells indicates excessive estrogen, and/or

expression of cyclin E of greater than 1+ staining intensity in the cytoplasm of greater than 10% of the gland cells indicates excessive estrogen; and/or

expression of p27 in the nuclei of less than 20% of the gland cells indicates deficient progesterone.

55. The method of claim 54 wherein the expression of cyclin E and p27 is detected by an immunohistochemisty assay.

56. The method of claim 54 further comprising the step of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample.

57. The method of claim 54 further comprising the step of detecting the expression MAG in the gland cells in a serial section of the sample wherein expression of MAG in greater than 10% of the gland cells indicates excessive estrogen or insufficient progesterone.

58. The method of claim 54 further comprising the steps of detecting the expression of progesterone receptor in the gland cells in a serial section of the sample and detecting the expression of MAG in the gland cells in a serial section of the sample.

59. The method of claim 54 further comprising the step of adjusting the hormonal protocol following evaluation.

60. The method of claim 59 further comprising the step of repeating the evaluation method following the adjusting of the hormonal protocol.

61. A method of diagnosing endometrial glandular mitotic arrest in a woman suspected of having endometrial hyperplasia comprising the step of:

detecting expression of cyclin E in the nuclei and/or the cytoplasm of endometrial gland cells in an endometrial tissue sample from said woman;

detecting expression of p27 in the nuclei an of endometrial gland cells in serial section of said endometrial tissue sample;

wherein

expression of cyclin E in the nuclei of less than 10% of the gland cells and expression of p27 in the nuclei of greater than 10% of the gland cells indicates endometrial glandular mitotic arrest.

62. The method of claim 61 wherein the expression of cyclin E and p27 is detected by an immunohistochemisty assay.

63. The method of claim 62 wherein a histological evaluation indicates possible hyperplasia.

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